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Know Your Limits: The Role of Boundaries in the Development of Spatial Representation

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In this issue of *Neuron*, Bjerknes et al. (2014) show that cells responding to environmental boundaries (border/boundary cells) are present as soon as rat pups can independently explore their environment. These boundary-based representations may thus provide a scaffold for other, later emerging, spatial representations.

Spatial cells in the hippocampal formation probably provide the substrate for a "cognitive map" supporting spatial memory and navigation (O'Keefe and Nadel, 1978). To date, four distinct classes of spatial cell (reviewed in Hartley et al., 2014) have been identified (see Figure 1A, right). Place cells fire whenever the animal passes through a circumscribed region of its environment; head direction (HD) cells fire when the animal faces a particular allocentric direction (e.g., northeast); grid cells fire in a highly regular pattern in which uniformly spaced fields form an equilateral triangular grid, tessellating the environment; boundary or border cells have extended fields that follow the boundaries of the environment in a particular allocentric direction such that a given cell might fire along the southern perimeter of an arena, for example (e.g., Figure 1A, bottom right).

Research groups are now turning their attention to unresolved questions about the nature of functional interactions between the different cell types. For instance, since grid cells are found in superficial layers of medial entorhinal cortex (MEC) that project to the hippocampus proper where place cells are located, several models (see Hartley et al., 2014 for review) have suggested that place fields might be understood as summations of input from multiple grid cells. However, there has been little direct evidence that functioning grid cells are necessary for place field formation, and indeed evidence has emerged against this view. For example, Koenig et al. (2011) showed that pharmacological inactivation of the medial septum abolished the spatial periodicity of grid cells but left spatial properties of place cells largely intact.

An alternative and increasingly influential approach addresses the causal dependencies between the different types of spatial cell by investigating the maturation of spatial codes in developing animals (reviewed in Wills et al., 2014). Two such studies (Langston et al., 2010; Wills et al., 2010) showed that stable hippocampal place fields develop well before stable periodic grid fields in MEC (and that HD cells are mature before both these cell types; see Figure 1A, left). So if grid cells are not driving place cell firing fields, where is the place cells' spatial signal coming from?

The new study by Bjerknes and colleagues (2014) shows that border cells—defined here as cells with elongated firing fields in contact with a parallel environmental boundary—are present in MEC from the earliest stage (around the age of 16–18 days) at which spatial cells can be recorded as the rat first moves freely around its environment. This important result emphasizes environmental geometry, as coded by such cells, as an alternative source of spatial information that might underlie the emergence of place cells. So an important question is: what is the quality of spatial signal coming from these early border cells?

The core properties of border cells are established early and do not change greatly in older animals. Bjerknes et al. (2014) find no sign that the proportion of entorhinal cells classified as border cells changes across the age range investigated (from 16 days to adulthood). Critically, the across-trial and within-trial reproducibility of spatial fields in early-appearing border cells appear robust and show no significant change in field stability with age. The already reliable boundary-related response shows signs of increasing spatial specificity in more mature animals, as spatial fields sharpen with age: the spatial coherence (correlation between the firing rates observed at neighboring locations) and spatial information content of firing fields increase while field sizes decrease. Replicating previous developmental results (Langston et al., 2010; Wills et al., 2010), HD cells are found from the youngest age group onward, but stable adult-like grid cells are not seen until much later.

Bjerknes et al. (2014)'s latest results, together with the evidence outlined above that place cell firing is not causally dependent on the spatial signal from grid cells, give new impetus to older ideas concerning the relationship between place fields and environmental geometry. O'Keefe and Burgess (1996) showed that place cells fired in "corresponding" locations (e.g., "northwest corner") in environments that differed only in shape and size. They explained these results by positing "boundary vector cells" (BVCs; Hartley et al., 2000) as inputs to the hippocampus. Each BVC would fire maximally whenever the animal was at a specific distance and direction from an environmental boundary (see Figures 1B–1D). By combining inputs from several such cells, the consistency of place fields across changes of environmental geometry could be explained and a place cell's firing in novel environments could be predicted. However, when empirical reports of cells with the anticipated characteristics began to emerge (Barry et al., 2006;

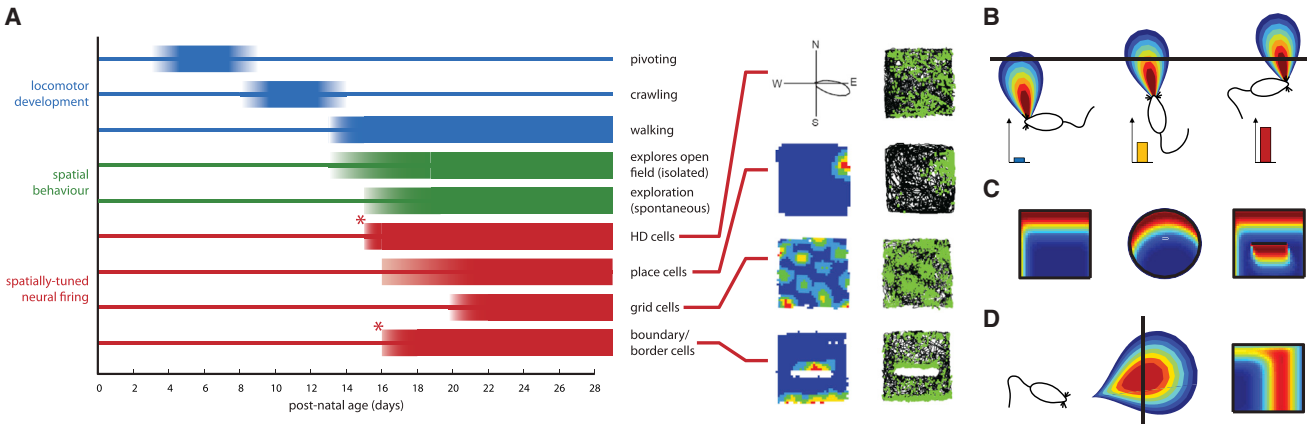

Figure 1. Development of Boundary-Related Neural Responses in Rat Hippocampal Formation and BVC Model

(A) Left: development of spatial firing in the hippocampal formation of the rat with relevant motor and behavioral milestones. Schematic is based on Wills et al. (2014) and incorporates Bjerknes et al. (2014). "*" indicates recordings of HD and border cells in younger animals have not been reported. Right: examples of spatial firing fields for each cell type (adult rats, see Hartley et al., 2014 for more detail): rightmost plots: black line shows path of rat exploring a square arena, green dots show where spikes were recorded; leftmost plots: corresponding firing rate maps (higher firing rates → hotter colors). Head direction cells do not show locationally specific firing; instead the directional firing field is plotted on polar axes with radial extent of the firing field (black line) showing mean firing rate when the rat is facing the indicated direction.

(B) The BVC model (Hartley et al., 2000) anticipated cortical inputs to the hippocampus that would show boundary-related firing as the rat approaches a barrier or edge at a specific distance and allocentric direction from the rat.

(C) Characteristic spatial firing fields when the BVC's receptive field (above) interacts with the boundaries of different environments. In this case, an elongated field runs parallel to the northern perimeter regardless of the shape of the environment, with an additional field appearing south of a short barrier inserted into the environment.

(D) The BVC model also included long-range boundary cells with broader tunings firing when the rat is at some distance from the environmental boundaries.

Lever et al., 2009; Savelli et al., 2008; Solstad et al., 2008), the importance of the newly discovered border or boundary cells relative to grid cells was unclear. Bjerknes et al. (2014)'s findings provide further support for the model's central prediction that hippocampal place fields depend on cortical inputs with the signature response to environmental boundaries, but they also raise new questions about the properties of this least-studied class of spatial cells.

In particular, the BVC model had postulated the existence of cells responding to more distant boundaries (which would be less numerous but more broadly tuned; see Figure 1D), whereas most empirically observed cells described to date fire when only the rat is very close to the edges of its environment. Bjerknes and colleagues (2014) point out that without relatively long-range inputs, it is unclear how place fields could form at more central locations. They argue that border cells might contribute principally to place fields near the perimeter of the environment, while place cells with more central fields might depend on input from late-developing grid cells. Indeed, preliminary data from the Cacucci/Wills lab (Cacucci et al., 2013, Soc. Neurosci., abstract) indicates that hippocampal place field stability is inversely correlated with distance from environmental boundaries in pups until around the time that grid cells mature. In this context, an additional function of grid cells becomes clear; by exploiting self-motion information and attractor dynamics (e.g., McNaughton et al., 2006), they may enable location-diagnostic information provided by stable geometrical cues at the edges of the environment to be extrapolated into areas where such cues are remote and thus less reliable.

It will be important, then, to clarify the role of longer-range boundary-sensitive spatial cells (Figure 1D). A few such cells have been identified in the subiculum (Lever et al., 2009), and other possible examples can be found in earlier studies investigating MEC cells (Koenig et al., 2011; Solstad et al., 2008). Their firing fields are necessarily further from the boundaries to which they respond and they are also likely to be more diffuse than those of short-range border cells and to convey less spatial information. More sensitive methods may thus be needed to identify and characterize cells with distal-to-boundary firing. Since spatial cells show larger spatial scale ventrally (e.g., larger place fields and larger, more widely spaced grid fields), it is also conceivable that more broadly and distally tuned boundary cells will be found in sites more ventral than those typically sampled in MEC recording studies.

While Bjerknes et al. (2014)'s results suggest a causal role for boundary cells in place field formation, the nature of developmental and causal relationships between boundary cells and other spatial cell types remains to be investigated. However, the latest results already indicate an early causal role for directional information: most boundary cells do not fire to any and all boundaries but only to those lying in a particular direction. For example, a cell responding to the northern boundary of the environment will also fire on the south side of an east-west-oriented barrier (see Figure 1C, right). Indeed, Bjerknes et al. (2014) report a robust and directionally specific response to barrier insertion at the earliest point that border cells can be observed, so it seems likely that the stable directional reference provided by early maturing HD system

is, from the outset, a necessary precursor for border cell expression. Future work will need to explore the likely intriguing interactions between boundary cells and grid cells. In adult animals, it is increasingly evident that, like place cells, grid cells are sensitive to environmental geometry (Barry et al., 2007). Strong new evidence for this influence comes from one recent report (Stensola et al., 2013, Soc. Neurosci., abstract) showing that grid field orientations can be clustered around common axes in different animals when recorded in the same environment. An open question, then, is when does this link arise developmentally? Is it, as seems likely, mediated by boundary cells? For example, can it be disrupted by their selective inactivation?

In summary, Bjerknes et al. (2014)'s findings shed new light on the way that allocentric spatial representation develops in the hippocampal formation. They indicate that boundary cells provide early stable cues to location, at a stage of development when stable place and grid representations have yet to be established. This suggests that the later-maturing place cells and grid cells may initially depend on early-maturing boundary and HD cells for their allocentric stability. One interpretation of grid cell function suggested by this process is that development of reliable grid fields is needed to allow the geometry of the environment to exert its anchoring influence at locations that are remote from boundary itself, supporting more central place fields. Overall, the study provides a powerful new demonstration of the value of the developmental approach in providing causal constraints on interactions between different forms of neural representation.

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Strippers Reveal Their Depressing Secrets: Removing AMPA Receptors

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How do microglia regulate synaptic function? In this issue of *Neuron*, Zhang et al. (2014) describe a novel form of long-term depression of AMPA receptor-mediated synaptic transmission in the hippocampus involving the activation of microglia.

Microglia, the immunocompetent cells of the CNS, are involved in numerous diseases of the nervous system (Hagberg et al., 2012; Perry and Teeling, 2013). In response to insults, they change from a monitoring to an activated state in which a major function is the phagocytosis of damaged tissue. Microglia are in dynamic contact with neurons, where they also serve to either promote or inhibit neuronal survival. One critical function of activated microglia is to remove dysfunctional synapses, via a process termed "synaptic stripping" (Kettenmann et al., 2013). It is likely that these mechanisms operate both under physiological conditions, in particular for the pruning of superfluous synapses during development (Paolicelli et al., 2011; Schafer et al., 2012), as well as under pathological conditions to eliminate synapses of damaged neurons. Clearly, a process that functions to eliminate synapses needs to be tightly regulated.